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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/518,190	03/02/2000	John Edward Hesketh	0623.0820001/REF	4790
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STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C. 1100 NEW YORK AVE., N.W. WASHINGTON, DC 20005			EXAMINER LANDSMAN, ROBERT S	
			ART UNIT 1647	PAPER NUMBER 22

DATE MAILED: 10/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/518,190

Applicant(s)

HESKETH ET AL.

Examiner

Robert Landsman

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9-16,21,23-26 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) _____ is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. Formal Matters

- A. Amendment E, filed 7/10/03, has been entered into the record.
- B. Claims 9-16 and 21 were pending in the Application. In Amendment E, Applicants added new claims 23-26. Therefore, claims 9-16, 21 and 23-26 are pending and are the subject of this Office Action.
- C. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Claim Rejections - 35 USC § 112, first paragraph –scope of enablement

A. Claims 9-16 and 21 remain rejected under 35 USC 112, first paragraph, and new claims 23-26 are also rejected for the reasons already of record on pages 2-4 of the Office Action dated 4/10/03. Applicants argue that this rejection had already been overcome by their previous arguments and are unsure as to why this rejection has been made again. Applicants argue that the present invention establishes that the addition of a nucleic acid encoding a signal peptide sequence to an mRNA encoding an intracellular protein is not sufficient to target that mRNA to the ER and that it is necessary to disrupt the 3'-UTR of the mRNA. Applicants also argue that the Examiner's objections on page 3 of Paper No. 8 are with regard to the portion of the 3'-UTR that can be altered, but that Applicants claim that the entire 3'-UTR can be deleted and that page 4, lines 15-19 of the specification show that this can be determined without undue experimentation. Applicants argue that, in contrast to the Examiner's assertions, one need not know which residues are required to allow the targeting to the desired locations in the cell and that the Examiner had stated that one of ordinary skill in the art would know whether the 3'-UTR has been sufficiently disrupted to negate its intracellular targeting effects.

The reason this rejection was withdrawn in the previous Office Action was due to the fact that one of ordinary skill in the art would know whether the 3'-UTR has been sufficiently disrupted to negate its intracellular targeting effects. However, upon further review of the specification and Applicants' arguments in previous Actions, it was determined that the effect of the disruption of the 3'-UTR on mRNA signaling was unexpected and Applicants were only able to achieve their desired result of redirecting the mRNA by removing the entire UTR. Therefore, given this unexpected results, the rejection was reinstated, but altered, to state that Applicants are enabled only for the unexpected finding that ***completely*** disrupting the 3'-UTR of rabbit beta globin and ***replacing it with the entire 3'-UTR*** of c-myc

Art Unit: 1647

or albumin produced the desired results. Therefore, Applicants have only provided guidance and one working example. Therefore, given the unexpectedness of this finding and only this one example, the breadth of the claims is excessive with regard to Applicants claiming disrupting the 3'-UTR of any protein whose targeting was intended to be altered. Again, Applicants have only shown that completely deleting the entire 3'-UTR produced the desired effects. Therefore, this limited example combined with the fact that Applicants have not demonstrated what regions of the 3'-UTR could be altered, other than for removal of the entire region, led the Examiner to reinstate a similar rejection to the one of Paper No. 8. Due to this lack of guidance and only one example, it would not be predictable to the artisan which bases to alter in the 3'-UTR of any mRNA, other than removal of the entire region, in order to produce the desired effect of redirecting the mRNA.

Therefore, in summary, the breadth of the claims is excessive with regard to Applicants' claiming any and all nucleic acid molecules which can have any and all alterations to its 3'-UTR in order to redirect its intracellular pathway. Applicants have only shown that completely disrupting the 3'-UTR of rabbit beta globlin and replacing it with the entire 3'-UTR of c-myc or albumin produced the desired results. Therefore, due to the lack of guidance and working examples of redirected molecules with altered 3'-UTRs, it is not predictable to the artisan which regions of the 3'-UTR to alter in order to achieve the desired result. Therefore, undue experimentation is required to practice the invention as claimed (i.e. as written).

While Figure 3 has been made more clear by Applicants' explanation, and this is appreciated, it still remains unclear why it appears in Figure 3 and 6B that the mRNA is found in the free and cytoskeletal fraction, which implies that the encoded protein would "normally" be secreted. Furthermore, though it appears in Figure 6B that the localization of the mRNA to the membrane fraction is reduced, it is not clear that these molecules are being redirected, (i.e. there is no % increase in either free or cytoskeletal polysomes) only that there is a decreased amount in the membrane-bound polysomes, which does not imply that the encoded proteins are being secreted.

3. Claim Rejections - 35 USC § 103

A. Claims 9-16 and 21 remain rejected under 35 USC 103 for the reasons already of record on pages 4-5 of the Office Action dated 4/10/03. Applicants argue that Hesketh et al. only teach the retargeting of mRNA between free and cytoskeletal-bound polysomes and does not teach retargeting the protein to membrane-bound polysomes. This argument has been considered, but is not deemed persuasive. Hesketh

and new claims 23-26 are also rejected

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Art Unit: 1647

do teach that "it is already well-known...that directional information for mRNAs is...present in their 3'-UTR. Applicants argue that Figure 2 of Hesketh do not demonstrate that anyone knew of directional information being present in the 3'-UTR. However, Figure 2 makes it clear that, in fact, alteration of the 3'-UTR by replacing the c-myc UTR with that of globin did increase the amount of transcript targeted to the membrane-bound polysomes and a smaller amount targeted to the cytoskeletal-bound polysomes. Therefore, it appears that Hesketh do teach that altering the 3'-UTR can redirect transcript to membrane-bound polysomes. Though Applicants argue that Hesketh do not teach using a signal sequence, Sleep do teach this sequence. Given the fact that Figure 2 of Hesketh demonstrate that altering the 3'-UTR can promote the targeting of transcript to membrane-bound polysomes, it would have then been obvious to aid in the expression of the encoded proteins by adding a signal sequence to the mRNA targeted to the ER (membrane-bound polysomes) since it was well-known in the art, as taught by Sleep, that signal sequences, such as serum albumin, aid in the expression of proteins. These proteins are inherently expressed from translation in the ER, where the transcripts of Hesketh are directed upon alteration of their 3'-UTR. Therefore, regardless of whether or not Sleep teach that the signal sequence could compete with the 3'-UTR for targeting, it would still have been obvious given the independent teachings of Sleep and Hesketh. In order for the present invention to be obvious, Sleep would not need to teach the 'conflict' between the signal sequence and the 3'-UTR since it was already clear by the teachings of Hesketh that the 3'-UTR could be altered to alter message targeting. Therefore, all one had to do was to use the general knowledge of the artisan at the time to realize that, since mRNA can be targeted to the ER by altering its 3'-UTR (Hesketh) then the addition of a signal sequence would aid in the protein's secretion. It is believed that all pertinent arguments have been addressed.

4. Conclusion

A. No claim is allowable.

Art Unit: 1647

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
October 02, 2003


ROBERT LANDSMAN
PATENT EXAMINER